DRUG DELIVERY—TOPICAL AND TRANSDERMAL ROUTES

Kenneth A. Walters
An-eX Analytical Services Ltd, Cardiff, United Kingdom

INTRODUCTION

Over the past 3 decades there have been significant advances in the science of dermal and transdermal drug delivery. Much of this research has been reviewed and published elsewhere (1–9). This chapter, therefore, will concentrate on more recent innovations and research directions. The author recognizes that the review will not be exhaustive and apologizes unreservedly for any omissions, either deliberate or accidental. Thus, the reader interested in the recent developments in physical methods of skin permeation enhancement, such as iontophoresis, electroporation, and sonophoresis, is directed to the excellent reviews of Banga (5), Lai and Roberts (10), and Kost et al. (11), and the research papers of Guy et al. (12), Ilic et al. (13), and Lombry et al. (14). Likewise, detailed descriptions of the formulations used in dermal and transdermal drug delivery will be omitted because they are fully discussed elsewhere (4). Mathematical aspects of percutaneous absorption and its prediction will be briefly mentioned but readers wishing to delve into the complexities of this subject should consult the detailed analyses of Pugh et al. (15) and Roberts et al. (16). This chapter will concentrate on recent developments in our understanding of the skin barrier and the novel chemical methodologies used to reduce barrier function. Technologies that may be useful in reducing adverse local reactions, often associated with dermal and transdermal drug delivery, will be discussed. There will be a brief review on innovative drug delivery systems. Finally, the recent regulatory initiatives in dermatological therapy will be described.

STRATUM CORNEUM DEVELOPMENT, MICROSTRUCTURE, AND BARRIER FUNCTION

Stratum Corneum Development

The development of the stratum corneum involves several steps of cell differentiation, which has resulted in a structure-based classification of the layers above the basal layer (the stratum basale). Thus, the cells progress from the stratum basale through the stratum spinosum, the stratum granulosum, and the stratum lucidium to the stratum corneum (17). Cell turnover from stratum basale to stratum corneum is estimated to be on the order of 21 days. The exact mechanism underlying the initiation of keratinocyte differentiation is not fully understood. It is known that protein kinase C and several keratinocyte-derived cytokines may play a regulatory role in the differentiation process (18, 19).

In the outer cell layers of the stratum spinosum, intracellular membrane-coating granules (100–300 nm in diameter) appear within the cells. Within these granules lamellar subunits arranged in parallel stacks are observed. These are believed to be the precursors of the intercellular lipid lamellae of the stratum corneum (20, 21). In the outermost layers of the stratum granulosum the lamellar granules migrate to the apical plasma membrane where they fuse and eventually extrude their contents into the intercellular space (20). The extrusion of the contents of lamellar granules is a fundamental requirement for the formation of the epidermal permeability barrier (22, 23). Thus, the entire process of epidermal terminal differentiation is geared toward the generation of the specific chemical morphology of the stratum corneum. As a result, the end products of this process are the intracellular protein matrix and the intercellular lipid lamellae.

The cornified cell envelope is the outermost layer of a corneocyte, and mainly consists of tightly bundled keratin filaments aligned parallel to the main face of the corneocyte. The envelope consists of both protein and lipid components in that the lipid is attached covalently to the protein envelope. The envelope lies adjacent to the interior surface of the plasma membrane (24). The corneocyte protein envelope appears to play an important role in the structural assembly of the intercellular lipid lamellae of the stratum corneum. The corneocyte possesses a chemically bound lipid envelope comprised of *N*-ω-hydroxyceramides, which are ester linked to the numerous glutamate side chains provided possibly by both the α-helical conformation and β-sheet conformation of involucrin in the envelope protein matrix (25, 26). In the absence of *N*-ω-hydroxyceramides, the stratum corneum intercellular lipid lamellae were abnormal and permeability barrier function was disrupted (27).

The Intercellular Lipids

The stratum corneum intercellular lipids exist as a continuous lipid phase occupying about 20% of the stratum corneum volume and arranged in multiple lamellar structures. They are composed of cholesterol (27%) and ceramides (41%), together with free fatty acids (9%), cholesteryl esters (10%) and cholesteryl sulfate (2%) (28) (Table 1). Phospholipids, which dominate in the basal layer, are converted to glucosylceramides and subsequently to ceramides and free fatty acids, and are virtually absent in the outer layers of the stratum corneum. Eight classes of ceramides have been isolated and identified in human stratum corneum (29, 30) but the functions of the individual ceramide types are not fully understood. Similarly, the exact function of cholesterol esters within the stratum corneum lamellae is also elusive but it is theoretically possible that cholesterol esters may span adjacent bilayers and serve as additional stabilizing moieties.

Overall, the intercellular lipid lamellae are highly structured, very stable, and constitute a highly effective barrier to chemical penetration and permeation. Considerable information on lipid structure within the stratum corneum has been generated by Bouwstra, Ponec, and colleagues using small angle X-ray diffraction and transmission electron microscopic techniques. These and earlier studies have shown that the lipid lamellae of the stratum corneum are orientated parallel to the corneocyte surface and have repeat distances of approximately 6.0–6.4 mm and 13.2–13.4 nm. In more recent studies on lipid packing (31), the Leiden group evaluated lipid organization of the stratum corneum using electron diffraction and found that although the majority of lipids in the intercellular space were present in the crystalline state, there were some lipids existing in the gel state that had a slightly looser hexagonal packing arrangement in the outer layers of the stratum corneum.

Table 1 Lipids of the stratum corneum intercellular space

Lipid	wt%	mol%
Cholesterol esters	10.0	7.5[a]
Cholesterol	26.9	33.4
Cholesterol sulphate	1.9	2.0
Total cholesterol derivatives	38.8	42.9
Ceramide 1	3.2	1.6
Ceramide 2	8.9	6.6
Ceramide 3	4.9	3.5
Ceramide 4	6.1	4.2
Ceramide 5	5.7	5.0
Ceramide 6	12.3	8.6
Total ceramides	41.1	29.5
Fatty acids	9.1	17.0[a]
Others	11.1	10.6[b]

[a]Based on C16 alkyl chain.
[b]Based on MW of 500.

Stratum Corneum Barrier Properties

Systematic evaluation of the skin permeability of many compounds has demonstrated that the intercellular lipids of the stratum corneum are essential for normal skin barrier function. It is clear that the major route of permeation across the stratum corneum is through the continuous intercellular lipid lamellae. Thus, the rate at which permeation occurs is largely dependent on the physicochemical characteristics ofthe penetrant, the most important being the relative ability to partition into the intercellular lipid lamellae and molecular size. Three major variables account for differences in the rate at which different compounds permeate the skin: the concentration of permeant applied, the partition coefficient of the permeant between the applied vehicle and the stratum corneum, and the diffusivity of the compound within the stratum corneum. A plot of the log of the skin permeability rate versus permeant lipophilicity is usually sigmoidal, and reflects the existence of both lipophilic and hydrophilic barriers. This suggests that compounds with partition coefficients indicating an ability to dissolve in both oil and water (i.e., log P of 1–3) would permeate the skin relatively rapidly. This has been confirmed for a variety of compounds. Data illustrating the skin permeability of various nonsteroidal anti-inflammatory agents are shown in Fig. 1 (32).

Mathematical Prediction of Permeation (Limitations)

Mathematical models relate skin permeability of exogenous molecules to physicochemical parameters of the permeant (octanol/water partition coefficients and molecular weight [a surrogate marker of molecular size]). Similar models for animal and human skin relate normalized equations of best-fit regressions based on:

$$\log P_{\text{calc}} = A + B\log K_{\text{o/w}} + C \cdot \text{MWt}$$

where P is the permeability coefficient, $K_{\text{o/w}}$ is the o/w partition coefficient, and MWt is the molecular weight.

Different values of A, B, and C have been derived depending on species (33) and dataset used (15). The models are significantly limited by the range of partition coefficients (log $K_{\text{o/w}}$ range -3 to ~ 6) and molecular weights (MWt range 18–765) of the datasets used, and

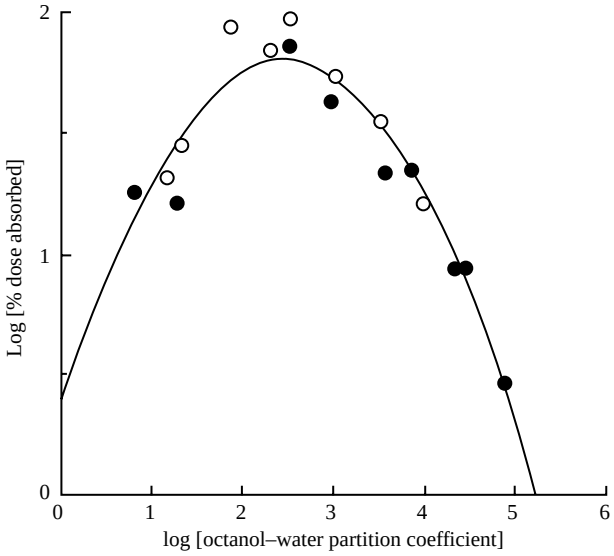

Fig. 1 Relationship between amount of drug absorbed though skin and compound octanol–water partition coefficient (increasing lipophilicity). Open circles: salicylates; closed circles: other nonsteroidal anti-inflammatory agents. (Redrawn from Ref. 32.)

anomalous values can be generated. As the boundaries of the dataset used are approached, the predictions become increasingly unrealistic. For example, the Vecchia equation (33) for human skin predicts that a permeant with molecular weight of 500 and log $K_{o/w}$ of 6 (not unusual for new drugs and cosmetic ingredients) will permeate skin at a rate of 1.3×10^{-2} cm/h, an order of magnitude faster than water or methanol. In addition, as these models are based on experiments in which permeants were applied in aqueous solution, their value in prediction of permeation from actual formulations applied under in-use conditions is further compromised. For example, while the predicted permeability coefficient for *N*-nitroso-diethanolamine is 1.5×10^{-4} cm/h, the experimentally determined value from isopropylmyristate was 3.5×10^{-3} cm/h (34). The predicted value for octyl salicylate is 1.35×10^{-7} cm/h, while the experimental values from a hydroalcoholic lotion were 4.7×10^{-6} cm/h (infinite dose) and 6.6×10^{-7} cm/h (finite dose), and from an oil-in-water emulsion 1.7×10^{-5} cm/h (infinite dose) and 6.6×10^{-7} cm/h (finite dose) (35).

Datasets continue to be accumulated and predictive methods continue to be refined. However, while mathematical predictions may be useful in the comparison of the behavior of closely related compounds, it is inappropriate to use them for risk assessment or formulation optimization purposes without relevant experimental verification.

CHEMICAL SKIN PERMEATION ENHANCEMENT

The success of dermatological or transdermal drug delivery systems depends on the ability of the drug to penetrate into and/or permeate through skin in sufficient quantities to achieve therapeutic levels. Over the past 2 decades, several chemical skin permeation enhancers have been designed, synthesized, and evaluated (1, 2). Many of these enhancers including Azone® (1-dodecylazacycloheptan-2-one) and SEPA® (2-*n*-nonyl-1,3-dioxolane) have been discussed in full elsewhere (36). Newer enhancers include 1-[2-(decylthio]ethyl)azacyclopentan-2-one (HPE-101), 4-decyloxazolid-2-one (Dermac™ SR-38), and dodecyl-*N*,*N*-dimethylamino isopropionate (DDAIP, NexACT 88) (Fig. 2).

HPE-101 is believed to have a similar mechanism of action to Azone and is very sensitive to the vehicle of application (37). Thus, although the enhancer significantly increased the urinary excretion of indomethacin following topical application to hairless mice, it was dependent on the application vehicle (37). When the enhancer was applied in solution in polar solvents, such as dipropylene glycol, triethylene glycol, diethylene glycol, glycerin, water, and triethanolamine, enhancement ratios varied between 1.5 and approximately 67-fold. However, when applied in solution in more lipophilic solvents, such as ethanol, isopropanol, oleyl alcohol, isopropyl myristate, or hexylene glycol, no enhancement was observed. These findings stress the importance of optimization of the delivery vehicle not only for the drug but also for the enhancer. Combinations of HPE-101 with cyclodextrins appear to be useful means to improve drug permeation across the skin (38). All of the available data, however, have been obtained

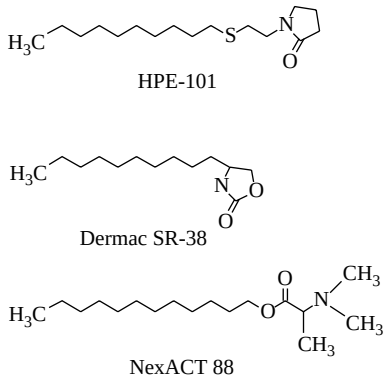

Fig. 2 Structures of the skin permeation enhancers HPE-101 (1-[2-(decylthio]ethyl)aza-cyclopentan-2-one), Dermac SR-38 (4-decyloxazolid-2-one), and NexACT 88 (dodecyl-*N*,*N*-dimethylamino isopropionate).

using hairless mice or other small laboratory animal skin. Small laboratory animals, especially the hairless mouse, can be uniquely sensitive to skin penetration enhancement and, as yet, the effectiveness of HPE-101 on human skin has not been reported.

Dermac SR-38 is one of a series of oxazolidinones, cyclic urethane compounds, evaluated as transdermal enhancers (39). The compound was designed to mimic natural skin lipids (such as ceramides), to be nonirritating, and to be rapidly cleared from the systemic circulation following absorption (40). In animal and human safety studies, Dermac SR-38 demonstrated a good skin tolerance (no observed irritancy or sensitization at levels of 1–10 wt%; moderate to severe irritation in rabbit at 100%), and a low degree of acute toxicity ($LD_{50(\text{rat oral})} > 5.0$ g/kg). The compound was evaluated for its ability to enhance the human skin permeation of diverse drugs from dermal and transdermal delivery systems. Data for minoxidil indicated an enhancer concentration-dependent effect for permeation enhancement. Dermac SR-38 was also found to enhance the skin retention of both retinoic acid when applied in Retin A cream, and dihydroxyacetone when applied in a hydrophilic cream (41).

NexACT 88 (dodecyl-*N*,*N*-dimethylamino isopropionate, DDAIP) is one of a series of dimethylamino alkanoates, reported to be biodegradable, which were developed as potential nontoxic skin permeation enhancers (42). Much of the early work was carried out using shed snake skin and it was found, using this model, that most of these compounds were equal to or more active than Azone. Studies using human skin indicated that dodecyl-*N*,*N*-dimethylamino acetate (DDAA) was a more effective enhancer of absorption of propranolol hydrochloride and sotalol than was Azone (43). Structural optimization of the compounds led to the identification of the lead candidate DDAIP (44), which appeared to be more effective than DDAA. Mechanism of action studies indicated that the distribution of DDAIP in stratum corneum lipids was somewhat different to that of DDAA, suggesting that other interactions were contributing to the penetration enhancement effect. It is possible that in addition to its effect on stratum corneum lipids, DDAIP may interact with keratin and potentially increase stratum corneum hydration.

Other compounds have been identified and have undergone preliminary evaluation as potential skin penetration enhancers. The data are, however, very limited and these candidate enhancers are mentioned here solely for completeness. The biodegradable fatty acid esters of *N*-(2-hydroxyethyl)-2-pyrrolidone (decyl and oleyl) were synthesized and evaluated for enhancer activity using hairless mouse skin (45). Permeation of hydrocortisone was enhanced two-fold. The activity of *n*-pentyl-*N*-acetylprolinate as a skin permeation enhancer has been determined using human skin (46). The enhancement potential of several sunscreen agents, including padimate O, octyl salicylate, and octyl methoxycinnamate, has been evaluated with some success (47). Table 2 lists some of the more recent patent disclosures concerning skin permeation enhancement.

Table 2 Recent patents containing references to skin permeation enhancers

Patent no.	Enhancer	Assignee
DE 19646050	Neohesperidinedihydrochalcone	Labtec
WO 9818417	Fatty acid esters of lactic acid salts	Theratech
WO 9817315	Polyethyleneglycol monoalkyl ethers	Alza
EP 98480674900	Crotamiton	Lab D'Hygiene et de Dietetique
EP 98440792145	Levulic acid	Lohmann
EP 98270665755	Polyglycolized glyceride	SmithKline Beecham
US 5723114	Proton pump inhibitors	Cellegy
US 5814599	Sonophoresis and liposomes	MIT
US 5885565	Sterols and sterol esters	Cellegy
US 5882676	Acyl lactylates	Alza
US 5879701	Oleic acid dimer; neodecanoic acid	Cygnus
US 5942545	Dioxolanes	MacroChem
US 6001375	Polyoxyethylene cetyl ethers	Gist-brocades
US 6001390	Methyl laurate; glycerol monolaurate	Alza
US 6019988	Dual carrier systems	Bristol-Myers Squibb
WO 9922714	Alkyl-(*N*,*N*-disubstituted amino) esters	Nexmed

ADVERSE LOCAL REACTIONS AND STRATEGIES FOR REDUCTION

Human skin is exposed to an environment that contains a variety of natural and synthetic compounds. Inevitably, dermal contact, either accidental or deliberate, will be made with a wide number of these compounds, many of which have the potential for inducing adverse cutaneous reactions, such as irritation and sensitization.

Adverse skin responses to chemical exposure are variable, may be immediate or delayed, and be of long or short duration. They may also be classified as irritant or allergic. Dermatological and transdermal formulations contain a complex mixture of active and inactive ingredients and it is important to appreciate that the cause of any adverse reactions may be a formulation additive (excipient) and not necessarily an active compound. Thus, for example, it is well known to those developing transdermal delivery systems that the pressure sensitive adhesive used to produce intimate contact with the skin is more likely to be the source of any cutaneous reactivity than is the drug. A further complication is that many of the inactive ingredients used in topical pharmaceutical dosage forms may have the ability to alter the barrier function of the skin, which in turn may enhance the percutaneous penetration not only of other formulation ingredients but also of subsequent exposure, either accidentally or deliberately, to chemicals.

Acute toxic contact dermatitis may be induced by a single application of a toxic material. One local inflammatory skin reaction is characterized by erythema and oedema. This type of reaction occurs following contact with materials such as acids, alkalis, solvents, and cleansers and is rarely associated with topical application of medicinal or cosmetic products. In contrast, irritant contact dermatitis (a superficial nonimmunologically based reaction) may occur after repeated exposure to many substances, including topical pharmaceutical agents. The reaction is usually localized to the site of exposure and usually diminishes after the stimulus has been removed. Some materials can stimulate an immune response following an initial topical application. Any future exposure may result in an inflammatory immune reaction, an allergic contact dermatitis, or sensitization.

There are two main sensitization reactions–immediate and delayed hypersensitivity. Immediate type hypersensitivity is the result of antibody–allergen interaction occurring in the skin; the reaction that develops is known as allergic contact urticaria. Delayed type hypersensitivity is the result of cell-mediated immunity and is the most frequently reported side effect of topical drugs. Both epidermal and dermal cells play pivotal roles in irritation and sensitization. Keratinocytes in the viable epidermis synthesize and secrete proinflammatory mediators and cytokines that activate the biochemical cascade leading to inflammation. Angiogenesis may also play a role in the inflammatory response but although it is possible that inhibitors of neovascularization may modulate the response to irritants, this hypothesis has yet to be fully investigated and is far from commercialization.

Before a compound can induce an adverse skin reaction upon dermal exposure, it has to penetrate into and permeate across the stratum corneum. Many of the strategies for the reduction of adverse reactions are based on reducing or modulating this process.

Retention of Compounds on the Skin (Reducing Penetration)

It is well established that a principle driving force for diffusion across the skin is the concentration, or more accurately the thermodynamic activity, of the permeant in the donor vehicle. Thermodynamic activity is reflected by the concentration of the permeant in the donor vehicle as a function of its saturation solubility within that medium. The closer to saturation concentration, the higher the thermodynamic activity and the greater the escaping tendency of the permeant from the vehicle. This principle has been extensively utilized in pharmaceutical formulation development in attempts to enhance percutaneous absorption of drugs but it is seldom used to reduce absorption. This is not surprising because for the most part, efficacy is improved by greater drug delivery to the therapeutic target. However, in some instances it is preferable to retain the active compound on the skin surface or within the outer layers of the stratum corneum (e.g., insect repellants and sunscreens) and this may be feasible using the vehicle thermodynamic activity approach.

Retardation of penetration can also be facilitated by the use of physical barriers such as protective creams and polymeric materials. There is evidence that emollient creams may be useful as skin barriers, although the results reported to date are somewhat variable and contradictory (48). More recently, however, convincing data have been presented that demonstrated that a barrier lotion containing the organoclay quaternium-18 bentonite (5%) was extremely effective in reducing the occurrence of allergic contact dermatitis to poison ivy and poison oak (49). Other polymeric materials are designed as skin compatible barrier materials. The latter materials include polyolprepolymer [Penederm Inc. (Bertek Pharmaceuticals)] and MacroDerms™ (MacroChem Corp.). Both types of polymeric

material have been shown to reduce the skin penetration and permeation of potentially irritating compounds.

The polyolprepolymer products are presently used in several cosmetics, over-the-counter, and prescription topical pharmaceutical products. An extensive toxicology package that illustrates that the polymers are safe in use is available. The polyolprepolymers are polyalkylene glycol-based polyurethanes and are available as three types (PP-2, PP-14, and PP-15) with varying solubility properties and associated formulation characteristics. They are, therefore, amenable to incorporation into a variety of formulation types, including gels, lotions, and creams. Convincing evidence indicates that the polyolprepolymers are capable of reducing the irritant response to retinoids in both laboratory animal and human models. In addition evidence has shown that these polymers are capable of modifying the skin distribution of applied materials, such as alphahydroxy acids and salicylates.

The MacroDerms is low to moderate (2000–25,000 Daltons) in molecular weight, symmetrical polymers that consist mainly of polyoxyethylene and polyoxypropylene linked by alkylene chains and end-capped by long alkyl groups (Fig. 3). The proportionality of the polymer chain mix renders hydrophobicity or hydrophilicity to the resultant block polymer. MacroDerm L, a lipophilic polymer consisting of two units each of 15 polyoxypropylene molecules linked by an alkylene group and end-capped by stearyl chains, has been shown to reduce the skin permeation of various sunscreen agents and pharmaceutically active compounds. A more hydrophilic MacroDerm, in which the polyoxypropylene chains of MacroDerm L

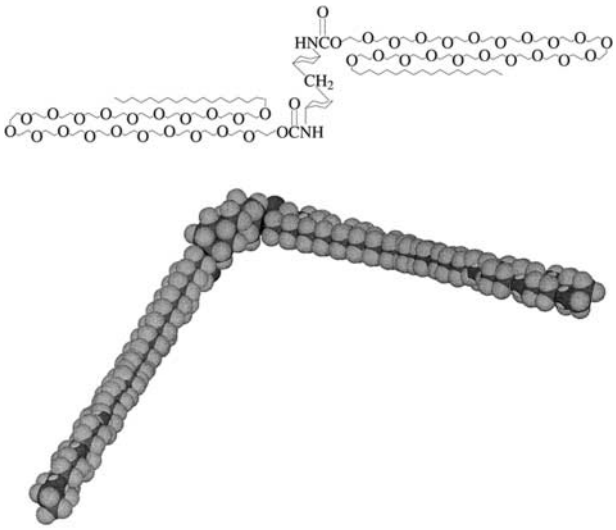

Fig. 3 Structure of MacroDerm SA20C (Courtesy of Dr. S. Krauser, MacroChem Corporation).

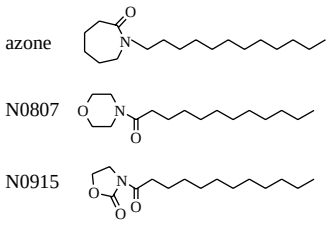

Fig. 4 Structures of Azone and the analogues N0807 and N0915.

have been replaced with polyoxyethylene chains, has been shown to increase the efficiency of a moisturizing formulation. The flexibility in the selection of moieties on the MacroDerm compounds suggests that they may be compatible with and easy to incorporate into a variety of topical formulation types. Given the structure of the MacroDerms and the nature of the constituent moieties (together with their similarities to existing compounds such as poloxamers and other nonionic surfactants), it is unlikely that there will be any safety issues associated with their use.

Reduction of Skin Diffusivity (Reducing Permeation)

The finding that an analogue (N0915) of the skin permeation enhancer Azone (Fig. 4) retarded the penetration of metronidazole through excised human skin, presumably by increasing the order (decreasing fluidity) of the intercellular stratum corneum lipids (50), led to a rationalization of the mechanism of enhancement at the molecular level (51). The structured nature of the stratum corneum intercellular lipid lamellae relies heavily upon lateral cooperative interactions between adjacent ceramide head groups. Enhancers such as Azone intercalate the matrix, but only provide a matching cooperative site on one side of the head group. On the other hand, the Azone analogue N0915, which has cooperative sites on both sides of the head group and retards permeation, while analogue N0807, which has electronegative sites on both sides of the head group, is a more effective enhancer than Azone. In addition, both Azone and N0807 have a preferred bent head group conformation which will disrupt packing of alkyl chains and increase the possibility of permeable defects. This basic concept was refined in the logical design of a series of molecules that were specifically targeted at retardation of skin permeation.

Experiments have been conducted on two of these compounds to determine their penetration retardation effect on two compounds, hydrocortisone and diethyl toluamide (DEET) (52). Fig. 5 shows that the retarders could reduced the permeation of hydrocortisone, while

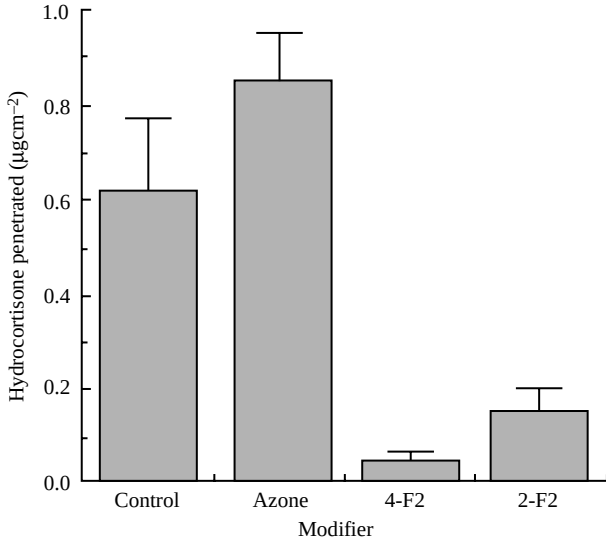

Fig. 5 Effects of Azone and the developmental retarding compounds 4-F2 and 2-F2 on permeation of hydrocortisone across human skin.

Azone, as expected, slightly increased permeation. Similarly, while Azone enhanced permeation of DEET, both retarder compounds reduced permeation. Although these data provide initial validation of the basic hypothesis for the mechanism of skin modulation, much remains to be accomplished before these compounds can be considered as viable strategies for irritation or sensitization reduction.

Miscellaneous Strategies for Modulating Skin Irritation

Many naturally occurring plant extracts are reputed to possess anti-irritant properties and have been recommended for use in cosmetic formulations. These include such diverse mixtures as tea tree oil, borage seed oil, Paraguay tea extract, Kola nut extract, oil of rosemary, and lavender oil. It is, however, difficult to standardize plant extracts and there may be a great deal of lot-to-lot variability in constituents. Understandably, this makes identification and isolation of any specific active constituent complex and laborious. The extracts may be oily or hydrophilic and contain compounds such as α-bisabolol, xanthines, polyphenols, and phytosterols. There is great potential in the use of plant extracts for irritation and sensitization reduction. This has been established within the cosmetic industry, and interest here has stimulated activity into reducing variability by more consistent cultivation techniques and more standardized extraction methods.

Strontium nitrate (Cosmederm-7™) has been shown to dramatically reduce the sensory irritation and erythema produced following application of a 70% free glycolic acid peel. It also has been shown to be effective in suppressing histamine-induced itch. Although the mode of action is unclear, the active principle appears to be elemental strontium in its free ionic form. It is postulated that the mode of action involves the potential ability of strontium to block neurogenic inflammation at type C neurons or nociceptors (53). It is interesting to note that the potential mechanism of action of strontium, involving nociceptor blockade, is also the mechanism by which capsaicin (the compound which renders chilli peppers "hot") is believed to provide relief in several painful conditions, such as pruritis, postherpetic neuralgia, and diabetic neuropathy. Various analogues of capsaicin have been synthesized and evaluated for anti-inflammatory activity with varying degrees of success (54). However, it is important to appreciate that although the strategy of blocking sensory neurones will inhibit the sensation of pain, it will not inhibit the inflammation associated with an irritation reaction.

A combination of compounds, including oleic acid, a short chain length alcohol, and a glycol, all gelled with a carbomer, has been found to reduce inflammation associated with the topical application of several chemical species (CELLEDIRM, Cellegy Pharmaceuticals, Inc.) (55). This formulation has been patented with the major claim that the use of a combination of oleic acid and glycerol provides skin penetration enhancement while reducing irritation potential (when compared with, for example, oleyl alcohol). CELLEDIRM has been shown to reduce inflammation by up to 40% in animal models challenged with potent irritants or allergens. All the excipient ingredients within CELLEDIRM are either generally accepted as safe (GRAS) status or have been used in various pharmaceutical or cosmetic products. Cellegy Pharmaceuticals plans to utilize CELLEDIRM in the development of several pharmaceutical, dermatological, and transdermal formulations.

NOVEL DELIVERY SYSTEMS IN DERMATOLOGICAL AND TRANSDERMAL THERAPY

In addition to traditional dermal and transdermal delivery formulations, such as creams, ointments, gels, and patches, several other systems have been evaluated. In the pharmaceutical semisolid and liquid formulation area, these include sprays, foams, multiple emulsions, microemulsions, liposomal formulations, transfersomes,

niosomes, ethosomes, cyclodextrins, glycospheres, dermal membrane structures, and microsponges (56–58). Many of these novel systems use vesicles to modulate drug delivery. Novel transdermal formulations include soft patches, microneedles, and powder delivery systems.

Semisolid Vesicular Systems

Mezei first suggested that liposomes may be useful drug carrier systems for the local treatment of skin diseases (59). The suggestion was based on drug disposition data obtained following topical application of the steroid triamcinolone acetonide incorporated in phospholipid liposomes formulated as lotions or gels. Encapsulation of triamcinolone acetonide into liposomes resulted in a vehicle-dependent 4.5- to 4.9-fold increase in the amount of drug recovered from the epidermis. The work of Mezei suggested that application of the dermatological drugs in liposomal form compared to conventional formulations led to increased drug concentration in the skin and subcutaneous tissues and decreased biodisposition in plasma and remote sites. These encouraging early observations were followed by several confirmatory research and clinical investigations, most notably those of Weiner's group at the University of Michigan (60) and Korting's group at Ludwig-Maximilians University in Munich (61). Many other studies have indicated the potential of phospholipid liposomes to increase the skin content of topically applied drugs. Liposomes also have been prepared from lipid mixtures similar in composition to the stratum corneum intercellular lipid (62).

Another vesicle system that has been investigated for potential modification of skin permeation are niosomes (63). Niosomes are composed of nonionic surfactants, such as polyoxyethylene alkyl ethers, and may be prepared as single or multilamellar vesicles. Surfactants of this type are known to enhance skin permeation and this is likely to play a role in any modification of permeation using these vehicles. The effect of nonionic surfactant vesicles on the skin permeation of estradiol was shown to be dependent on the physical state of the niosome. On the other hands niosomes prepared from polyoxyethylene(3)stearyl ether and existing in the gel state did not increase estradiol permeation, and those prepared from polyoxyethylene(3)-lauryl ether and polyoxyethylene(10)oleyl ether, both existing as liquid crystalline vesicles, significantly enhanced transport. Further experiments in which the skin was pretreated with unloaded niosomes indicated that the enhanced transport of estradiol from drug-loaded vesicles was not wholly a result of surfactant-induced penetration enhancement. The authors postulated that niosomes fused at the surface of the stratum corneum and generated high local concentrations of estradiol which resulted in increased thermodynamic activity of the permeant in the upper layers of the stratum corneum.

Vesicle systems, described as ethosomes composed of phospholipid, ethanol, and water, have been shown to enhance the transdermal delivery of minoxidil and testosterone when compared to more traditional formulations (Fig. 6) (57). The quantities of drug penetrating into and permeating through nude mouse skin in vitro were significantly greater from the ethosome systems than from appropriate control vehicles. Furthermore, when evaluated in rabbits in vivo, ethosomal transdermal patch systems produced higher testosterone plasma levels than a commercial patch. A tentative synergistic mode of action was proposed in which the ethanol disrupted the stratum corneum intercellular lipid, allowing the flexible ethosome to penetrate and possibly permeate the stratum corneum. The ethosome may subsequently fuse with skin lipids and release its drug content. The authors also point out that there may be a follicular contribution to the enhancement effect. It is interesting and important to note that there was no observed acute or cumulative irritancy (in rabbits) associated with the use of the ethosomal system.

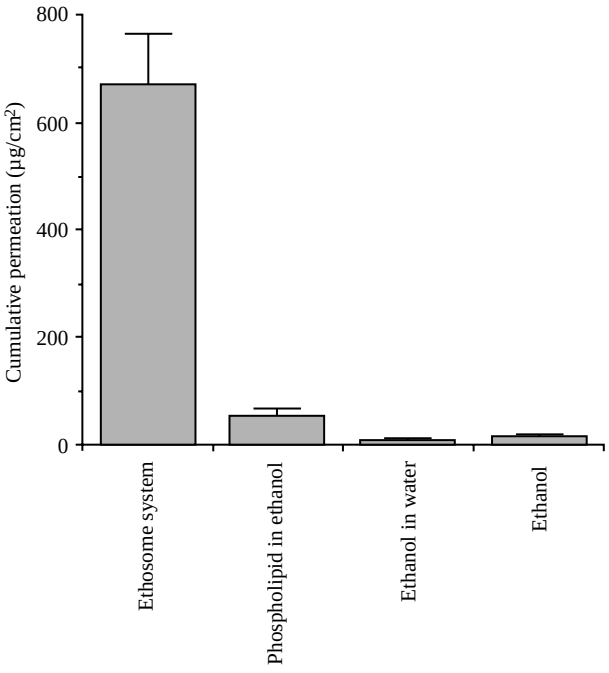

Fig. 6 Minoxidil permeation from ethosome systems and appropriate control vehicles. Data are expressed as the cumulative permeation across male nude mouse skin in vitro over 24 h. (Figure plotted from data given in Ref. 57.)

The precise mode of interaction between lipid vesicles and skin remains unclear. There is considerable doubt about the ability of whole vesicles to permeate intact stratum corneum. The majority of evidence suggests that vesicles can penetrate the outer cell layers of the stratum corneum where desmosomal linkages have become disrupted and presumably, the keratinocytes are less tightly bound and surrounded by a mixture of intercellular lipid and sebum. However, continuing diffusion of vesicles through the approximately 60 nm intercellular space of the deeper layers of the stratum corneum seems unlikely. Current thinking suggests that lipid vesicles fuse with endogenous lipid either on the surface or in the outermost layers of the stratum corneum. The fusion is followed by structural changes in the deeper layers of the stratum corneum, as evidenced by freeze-fracture electron microscopy and small angle x-ray scattering techniques. These structural changes are presumed to be the result of intercellular diffusion of vesicle lipid components (not intact vesicles) to the deeper layers, as well as interaction with and disruption of endogenous lipid lamellae. It is simple to postulate that this interaction/disruption of lipid lamellae will lead to an increase in skin permeation rates but this does not explain the observed increase in skin retention of permeants. Apparent increased skin retention may be an artefact from exogenous lipid depot formation on the skin surface. On the other hand, formations of lipid aggregates, possibly comprised of mixtures of endogenous and exogenous lipid, observed in deeper layers of the stratum corneum may provide a reservoir for topically applied drugs.

Cevc and Blume (64), however, suggested that it was possible for whole vesicles to cross intact stratum corneum. The basic premise for this hypothesis was the driving force provided by the osmotic gradient between the outer and inner layers of the stratum corneum and the development of specific mixes of lipids to form modified liposomes termed transfersomes. The requirement for the osmotic gradient to be maintained suggests that transfersomes will not function in occlusive conditions and careful formulation is necessary. Due to their unique structure (a mix of phosphatidyl choline, sodium cholate, and ethanol), transfersomes are reputed to be very flexible vesicles and capable of transporting their contents through the tortuous intercellular route of the stratum corneum. The application of the corticosteroids triamcinolone acetonide, dexamethasone, and hydrocortisone encapsulated in transfersomes resulted in more reliable site specificity for the drug and, therefore, less potential for adverse side effects (65).

Novel Transdermal Systems

In terms of overall composition, traditional transdermal patch systems have changed little in the past few years. The modifications that have been made are, for the most part, refinements of the materials used in their construction (Table 3). This is the case for the "soft" patches that consist of thin flexible films containing a known amount of drug (66). The soft patch is designed to be flexible and to conform to various body flexures.

Table 3 Recent patents containing references to transdermal materials

Patent no.	Material	Assignee
US 5783208	Pressure sensitive adhesive mixture	Theratech
WO 9820869	Electrotransport mechanism	Alza
US 5785688	Electromechanical gas generator	Ceramatec
WO 9737659	Crystallization inhibition	Sano
WO 9813099	Iontophoretic mechanism	Becton Dickinson
US 5753263	Liposomal formulation	Anticancer Inc.
WO 9813024	Hyaluronic acid	Hyal
US 5843979	Irritation/sensitization reduction	Bristol-Myers Squibb
WO 9832488	Irritation/sensitization reduction	Novartis
EP 98160665745	Pressure sensitive adhesive mixture	Lohmann
EP 98140716599	Crystallization inhibition	Lohmann
US 5843114	Skin perforation device	Samsung
US 5820875	Dual delivery rate device	Cygnus
US 5750138	Delayed onset of delivery	Westonbridge International
US 5713845	Laser-assisted drug delivery	ThermoLase
WO 9904838	Electromagnetic injection device	Boehringer Mannheim

Given the limitations imposed on transdermal systemic drug delivery by the barrier properties of the stratum corneum, new technologies have attempted to completely bypass this obstacle by either the creation of a physical conduit (microneedles) or direct powder delivery via compressed gas. The Alza Corporation technology (Macroflux™) comprises a patch system that contains a microprojection array designed to create superficial microchannels across the stratum corneum (67). When used in conjunction with their electrotransport system, the Macroflux system provides controlled in vivo delivery of therapeutic doses of antisense oligonucleotide, human growth hormone, and insulin. Similarly, the Redeon Inc. system consists of microfabricated microneedles that are150 μm in length and may be either solid or hollow (68). The Redeon system was effective in enhancing by several orders of magnitude the human epidermal permeability of calcein and bovine serum albumin (Fig. 7) (69).

Transdermal powder delivery uses a supersonic flow of helium to accelerate drug particles to velocities sufficiently high to penetrate the stratum corneum (70). The needle-free injection system is capable of painlessly delivering drugs and vaccines in powder form into the skin. The amount of drug delivered is related to particle size, dose level, and the device operating power. Recent data demonstrated that the powder delivery system was capable of delivering salmon calcitonin across rabbit skin in a dose-dependent (but nonlinear) manner (71). A similar system (the Helios™ gun system) was used to determine the effect of the dose regimen of a model drug incorporated into poly-*L*-lactic acid microspheres of varying particle size (72). It was concluded that more frequent applications that contain lower amounts of the model drug generated a superior plasma profile than larger drug loadings at less frequent dosage intervals.

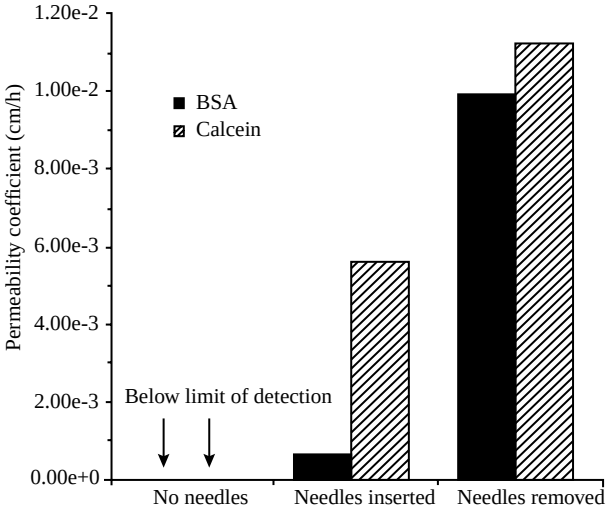

Fig. 7 Permeability of in vitro human epidermis to bovine serum albumin (BSA) and calcein. In the absence of microneedles, permeation was below the limit of detection. (Plotted from data given in Ref. 69.)

RECENT REGULATORY INITIATIVES

SUPAC-SS—Drug Release from Semisolid Formulations

Determination of the ability of a semisolid formulation to release a drug, the pattern of release and the rate at which this release, occurs are important aspects of formulation development and optimization. However, it is also important to appreciate that the data obtained should not be overinterpreted. Release studies normally involve the measurement of drug diffusion out of a mass of formulation into a receiving medium that is separated from the formulation by a synthetic membrane (73). A detailed analysis of the data obtained in this type of experiment can be expected to generate invaluable data concerning the physical state of the drug in the formulation. For example, an examination of the early models and their refined updates derived to describe drug release from semisolids reveals that release patterns are different depending on whether the drug is present as a solution or suspension within the formulation (74). These subtle differences, together with differences in the rate of release, may be used to determine such parameters as drug diffusivity within the matrix of a formulation, the particle size of suspended drug, and the absolute solubility of a drug within a complex formulation (Fig. 8) (75, 76). Although it is generally agreed that drug release rate data cannot be used to predict skin permeation or bioavailability, release rate determinations are important for purposes other than formulation development and characterization.

The Food and Drug Administration (FDA) has issued a guidance document (SUPAC-SS Nonsterile Semisolid Dosage Forms, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, May 1997) that recommends the use of in vitro drug release testing in the scale-up and postapproval changes for semisolids (SUPAC-SS). The FDA intends to promote the use of this test as a quality assurance tool to monitor minor differences in formulation composition or changes in manufacturing sites, but not at present as a routine batch-to-batch quality control test. Thus, the FDA is suggesting in vitro release rate data for Level 2 and Level 3 changes in formulation components

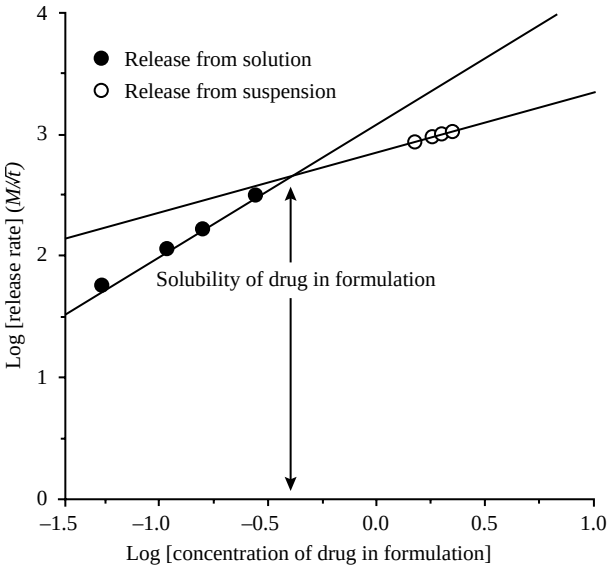

Fig. 8 Illustration of the use of release rates from semisolid preparations to determine drug solubility within a formulation. Data show the release rates of benzocaine from propylene glycol/water gels as a function of drug concentration in the formulation. (Redrawn from Ref. 75.)

and composition but such data are not required for a Level 1 change. In the former, the in vitro release rate of the new or modified formulation should be compared to a recent batch of the original formulation, and the 90% confidence limit should fall within the limits of 75–133%. Similarly, in vitro release testing is suggested for Level 2 changes in manufacturing equipment, processes, and scale-up, and Level 3 changes in manufacturing site. Recently, the use of in vitro testing as a quality assurance tool has been questioned, especially in the case of a hydrophilic formulation that contains the highly water soluble drug ammonium lactate (77). The method was found not to be specific enough to differentiate between small differences in drug loading or minor compositional and processing changes.

Bioequivalence of Dermatological Formulations

In practice, bioequivalence of dermatological dosage forms creates particular difficulties because it is often difficult to determine the very low blood levels of specific drugs following dermal application. The FDA has pioneered the use of alternative methods of evaluation including the investigation of dermatopharmacokinetics using the tape-stripping method. The use of in vivo skin stripping in dermatopharmacokinetic evaluation was the subject of an AAPS/FDA workshop concerning the bioequivalence of topical dermatological dosage forms (Bethesda, MD, September, 1996). Although opinion was somewhat divided, it was concluded that stratum corneum tape stripping "may provide meaningful information for comparative evaluation of topical dosage forms" (78). Furthermore, it was established that a combination of dermatopharmacokinetic and pharmacodynamic data could provide sufficient proof of bioequivalence "in lieu of clinical trials." However, much remains to be validated in skin stripping protocols. The in vivo tape stripping technique is based on the dermal reservoir principle developed by Rogier et al. (79). It is hypothesized that if a compound is applied to the skin for a limited time (for example 0.5 h) and then removed, the amount of drug in the upper layers of the stratum corneum will be predictive of the overall bioavailability of the compound. It follows that determination of the stratum corneum content of a permeating material following a short-term application will predict in vivo bioavailability from a corresponding administration protocol. Data obtained in studies of this type have shown reasonable predictability for several compounds.

An outline protocol for skin-stripping bioequivalence studies has been suggested (78). The basic protocol has two phases: uptake and elimination.

Uptake

1. Test and reference drug products are applied concurrently at multiple sites.
2. After exposure for a suitable time (determined by a pilot study), excess drug is removed by wiping three times with tissue or cotton swab.
3. The adhesive tape is applied with uniform pressure. The first strip is discarded (skin surface material). This is repeated if necessary to remove excess surface material.
4. Collect nine successive tape strips from the same site. If necessary collect more than nine strips.
5. Repeat the procedure for each site at designated time intervals.
6. Extract the drug from the combined tape strips for each time point and site and determine the content of drug using an appropriate validated analytical method.
7. Express the data as amount of drug per cm^2 of tape.

Elimination

1. Repeat steps 1, 2, and 3 "Uptake" phase.
2. After a predetermined time interval (e.g., 1, 3, 5, and 21 h postdrug removal) perform steps 4 through 7 of "Uptake" phase.

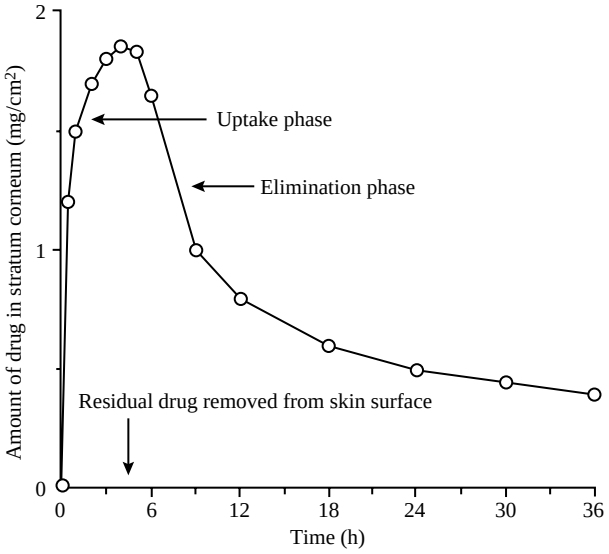

Fig. 9 Idealized dermatopharmacokinetic profile for a topically applied compound illustrating uptake and elimination phases. The amount of drug in the stratum corneum is determined by summing the total amount removed by tape stripping at each time interval.

The results are then expressed as the amount of drug recovered from the tape strips against time. Uptake and elimination phases are observed (Fig. 9) and bioavailability may be predicted from the area under the curve. There are several sources of variability in such studies, all of which must be considered in standard operating procedures. The major causes of concern in variability are:

1. drug application procedure
2. type of tape
3. size of tape
4. pressure applied by investigator
5. duration of application of pressure
6. drug removal procedure
7. drug extraction procedure
8. analytical methodology
9. temperature
10. relative humidity
11. skin type
12. skin surface uniformity

Other concerns have been expressed (80). These include the observation that vehicle components of the products to be evaluated may have different effects on the adhesive properties of the tape. In addition, it is important to appreciate that because the dermatopharmacokinetic bioequivalence studies will most likely be carried out on normal disease-free human volunteers, the generated data may show little resemblance to the actual drug distribution within the stratum corneum of patients. Nonetheless, following further validation, the technique will have several advantages. For example, basic pharmacokinetic parameters, such as AUC, C_{max}, T_{max}, and half-life, may be approximated from the data obtained. In addition, the approach could be applicable to all types of topical preparation.

Recently, Pershing (81) reviewed much of the extensive validation of typical in vivo skin stripping techniques. Such variables as the test region anatomical site, individual investigator technique, adhesive systems and product dose, application, and removal techniques were discussed. It was concluded that "careful validation of adequate removal of residual applied product, the collection of skin stripping samples and a sensitive analytical assay were critical to the appropriate interpretation of the results" (81). Further details of the dermatological drug product bioequivalence guidelines, including the proposed protocol, may be obtained from the FDA draft guidance document (Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, June 1998).

CONCLUDING REMARKS

The title of this article, *Drug Delivery—Topical and Transdermal Routes*, describes a field of pharmaceutical sciences that has expanded rapidly over the past 30 years. For example, it was only a few years ago that noninvasive transcutaneous immunization was only available on the 'Starship Enterprise.' Now the technology is available (82). To include all recent developments would require much more space than is feasible within the scope of this encyclopedia. Quite selfishly, therefore, I have elected to cover those subjects in which *I am* most interested. In partial mitigation, I have provided a reasonably complete bibliography and have attempted to point the reader who wishes to explore in more depth subjects not covered herein toward the most relevant recent references. Topical drug delivery, for either dermatological or transdermal therapy, is a fascinating subject, made more so by the nature of the skin. The more we understand the molecular biology of this unique organ, the more able we will be to fix it when it goes wrong. Similarly, a deeper understanding of skin barrier morphology will allow us to develop strategies to modify its permeation properties.

These are fundamental issues and improvement of our knowledge will increase our capabilities as drug delivery scientists. In this section, I have attempted to outline recent developments in the development of the stratum corneum and some of the methods used to modify the inherent barrier properties of this unique membrane. Some strategies for reducing adverse dermatological events associated with topical therapy have been discussed. Novel delivery systems were outlined and recent regulatory initiatives, which are planned to make life easier for the pharmaceutical industry, were described. I hope that my comments will provide the drug delivery specialist with some insights borne of experience and the experienced topical formulator with some alternative concepts in the field of dermatological and transdermal product development.

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